ACTA
NEUROBIOLOGIAE
EXPERIMENTALIS

Acta Neurobiol. Exp. 2003, 63: 163-170

Review

Unity from duality*

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Abstract. When, in the primeval sea, creatures first began to crawl, "right" and "left" came into being, yielding neuronal nets to control response to the sidedness of stimuli. In the half billion years of moving and sensing, two brains have evolved, the right and the left; and human experience now shows them to be roughly equivalent, potentially independent, conscious entities. This dramatic fact is evidenced by "split-brain" patients and by numerous cases of therapeutic removal of either hemisphere. Equally dramatic, of course, is that there is not the slightest sign of this duality in everyday experience, the right and left visual fields are seamlessly knit, and cross purpose is absent in the moment to moment operation of the two cerebral hemispheres. This unity is constantly synthesized by the 100,000,000 fibers passing from each hemisphere to the other; the vastness of that interchange emphasized upon comparison with the mere 1,000,000 fibers conveying all the visual world from each eye. With the large distances in the human brain some 100+ ms may commonly transpire for one hemisphere to send to and receive a response from the other. Efficiency thus demands that most neuronal calculation occur within rather than between hemispheres, thereby promoting differences in the characteristic capabilities of each alone, i.e., "hemispheric specialization". Despite this there is a bewildering bilaterality of activation revealed by fMRI for most cognitive tasks. In the absence of the forebrain commissures brainstem systems can be shown, in macaques, also to participate in the unification of behavioral result from the actions of the separated hemispheres. The system favors synthesis from congruent (visual) input to the two hemispheres; but in the face of incompatible hemispheric input, the two hemispheres are able to work out an accommodation in their control of subcortical systems.

Key words: laterality, commissures, corpus callosum, brainstem

*Dedicated to the memory of Jerzy Konorski, warm friend and great scientist, unflinchingly principled in an era beset by discord; and to his students, Wanda Wyrwicka and Bogusław Żernicki, whose uniquely creative pursuits I briefly shared.

BILATERAL SYMMETRY

There are many scenarios imaginable, but somehow a half billion years or so ago groups of cells got organized into metazoans (Brusca and Brusca 1990), found it advantageous to creep along the floor of the sea, to develop a head (encephalization), the ability to turn, right or left, and then receptors to steer the turning. This inevitably led organisms to choices, right, left or straight ahead, depending upon the signals from receptors and the nature of their coupling to the locomotor machinery. Remarkably, such a description is a close fit to Braitenberg's imaginary but crafty Vehicles (1984). The Vehicles possess an astonishing versatility despite the simplicity of their construction: positive *versus* negative coupling of receptors to motors, crossed or uncrossed to either side, and with differing types of receptors. Such Vehicles, as Braitenberg (1984) notes, are easily conceived; but observing only their behavior, it is astonishingly difficult to infer the underlying mechanisms as the Vehicles display their seeming "wants" and selections. But Braitenberg or Nature, the result, from Vehicle to flatworm to man, is a bilaterally symmetric control system (brain), having co-equal arrangements in either half (side) to guide an artifact or an organism through an environment evaluated by its receptors. In essence, the stage is set for decisions, harkening to the competing calls, or threats, from left or right.

Two things commonly escape notice in considering the ingenuity of this symmetrical patterning, a) being co-equal, each half of such a nervous system is potentially an independent entity; and thus, b) the necessity arises for one or the other side to decide which of two possible behaviors, that of the left or of the right, the organism will follow.

For instance, if in higher mammals the brainstem is transected longitudinally from mesencephalon to obex, swallowing will occur only on the stimulated side, although if both sides are stimulated concurrently, the act is coordinated bilaterally *via* fibers crossing posteriorly and rostrally to the transection (Doty et al. 1967). And, shades of some of the arrangements in Vehicles (Braitenberg 1984), the "half" swallowing center is organized to excite most of its half of the participating buccopharyngeal and laryngeal muscles (in proper sequence) ipsilaterally, but inhibit the ipsilateral pharyngeal constrictors; then belatedly excite the corresponding constrictors contralaterally. In other words, the temporally organized output, strangely, offers the constrictors first an inhibition ipsilaterally, but then decussates its excitatory control contralaterally. It would thus seem that there is a difficulty inherent in changing inhibition to excitation upon the same set of motoneurons by commands from the same controlling ensemble (the swallowing "half-center"); suggesting that it is more efficient or reliable if the switch from inhibition to excitation is achieved *via* different controlling entities, i.e., the two "half-centers". This illustrates, first, that the *raison d'être* for decussating pathways may lie in some still obscure physiological convenience and, second, that despite the independence of each half-center there remains a strong commissural linkage required for their normal coordination.

FOREBRAIN COMMISSURES

These principles apply with equal or greater force to the cerebral cortex, where the forebrain commissures, the corpus callosum and the anterior commissure provide intercommunication and coordination between the two hemispheres and, as noted below, each hemisphere is, potentially, an independent entity, with outputs both ipsi- and contralateral. The interhemispheric communication is relatively sparse. If one accepts 10^{10} as the total number of neurons in human neocortex and 2×10^8 fibers as the total in the corpus callosum (Aboitiz et al. 1992, Tomasch 1954), then 2% of the neurons project an axon to the contralateral hemisphere. Yet 2%, 2×10^8 is an enormous number, 100 times that of the population of retinal ganglion cells that sustain the richness of the entire visual world. Indeed, the enormity of the potential interchange between the two hemispheres defies ready understanding.

While, as briefly reviewed below, it is common knowledge that these callosal fibers are essential to coupling events in one hemisphere to those in the other, the neurophysiological detail as to how this is done is almost completely unknown. A population of cells in the circumstriate cortex supplies uniquely large axons that, presumably, account for the artful weaving of one visual field into the other (Shoumura et al. 1975), but the vast majority of callosal axons are <1 μm in diameter (Aboitiz et al. 1992, LaMantia and Rakic 1990). As a consequence, in brains of human size, there is an inevitable sluggishness in the pace of hemispheric interchange. This in turn must contribute greatly to the functional "specialization" of the two hemispheres in man, and perhaps other large brained creatures (Ringo et al. 1994). In other words, since the conduction velocity of the mostly small diameter callosal fibers is such as to require 50-100 ms or more for a two-way interhemispheric exchange, the constraints of time are such as to make it more efficient to perform multineuronal calculations along the shorter paths within a single hemisphere. Nature seems to have shrewdly calculated the compromise on axon size *versus* interhemispheric delay for, as Ringo (1991) has demonstrated, a doubling of the callosal conduction velocity *via* a doubling of callosal axon diameter would increase brain size by an astonishing 50%, the increased axon size itself requiring space, that enlarges conduction distances, etc!

Despite their sparseness and slow time course the forebrain commissures allow little trace of the underlying duality of the neuronal machinery. The efficiency of cross comparison is extremely high so that, for instance, items normally viewed in one visual field are well, and quickly, remembered when such items are then encountered in the other visual field (Kavcic and Doty 2002). The few faster fibers help with integration across the midline and blur the possibility of studying the two hemispheres individually in intact individuals. Most of the differences revealed by efforts to probe one *versus* the other hemisphere (divided visual fields, dichotic listening), are attributable to the functional specialization of the hemispheres, e.g., linguistic analysis by the left hemisphere, spatial relations by the right. The time frame of such experimental comparisons or interactions, however, is such that the basic slowness of cross hemispheric interaction is seldom challenged. This could be explored by continuously presenting differential input to the two visual fields (locking visual displays to movements of the eyes); but, of course, such an arrangement, where each hemisphere views a uniquely different visual scene, would also tax attention, so that the effect might merely be analogous to binocular rivalry (Blake and Logothetis 2002).

WHICH HEMISPHERE HAS THE ENGRAM?

Such experiments would be valuable in exploring whether true parallel processing could be achieved, whereby the two hemispheres could each simultaneously acquire different visual memories; but with forebrain commissures intact the testing would not reveal which hemisphere held which engram. The question would be equally as opaque as are divided visual field experiments in assigning location of memory traces or engrams when input is directed to only a single hemisphere. Regardless of the hemisphere initially addressed by the input, the trace may be bilateral, or limited to the initially viewing hemisphere and subsequently accessed, if necessary, *via* commissural mechanisms when the other hemisphere is confronted with the item; or the location may be apportioned according to the nature of the stimulus or task.

These conundrums have been reviewed by Doty and Ringo (1994). The answer seems to be that much depends upon the manner in which the input is manipulated. One of the more interesting situations arises with electrical excitation of the striate cortex in macaques (Doty et al. 1973). So long as the splenium of the corpus callosum was intact, six animals trained to respond to stimulation in one hemisphere did so equally to test stimulation of the other striate cortex; but if then the splenium was transected, completing interruption of the forebrain commissures, no response could be elicited from the "untrained" hemisphere, whereas responses were unperturbed to stimulation of the "trained" hemisphere. From this it was concluded that the engram was exclusively unilateral, residing and remaining on the "trained" side, but available to the other hemisphere *via* callosal connections. The implication was that the callosal mechanism, while fostering interhemispheric access to such unilateral engrams, failed to promote bilateral memory and, by suppressing redundancy, thus augmented the "mnemonic space" of the brain.

This conclusion is suspect, however, since data from "split-brain" patients demonstrate that each hemisphere retains excellent recognition of a broad range of experience acquired prior to the surgery (Sperry 1984, Sperry et al. 1979).The "unilateral engram" of the Doty et al. (1973) experiments may be partly attributable to the superposition of the electrical excitation upon the normal visual processing of the animal for, unlike the usual experiments with "split-brain" macaques, the optic chiasm was intact in this instance, and both striate cortices were engaged with normal visual input during the course of training. More telling may be the very fact that the stimuli were applied directly to the striate cortex, that in higher primates lacks direct callosal connections, and may thus fail to produce the expected callosal activation. On the other hand, in nine of nine animals in which the analogous experiment was performed, save that the anterior commissure was the transferring path, the interhemispheric transfer was perfect following completion of the transection. In other words, while the engram remained unilateral when the callosum was the available path, it was unequivocally bilateral in the case of the anterior commissure. Perhaps propagation of the excitation from striate cortex into the temporal lobe was able to engage commissural elements normally, whereas the callosal elements in circumstriate cortex were inadequately engaged during training (yet functioned perfectly during testing!).

However that may be, using normal visual input in macaques, and disrupting processing by tetanizing temporal lobe in one or the other hemisphere, Ringo (1993) was subsequently able to show: a) that bilateral visual engrams are produced even with unilateral visual input, b) that when a unilateral engram is produced it can be accessed by the other hemisphere, and c) that if a unilateral engram is artificially established initially, it becomes bilateral after an interval of a few seconds. Thus, while there are other examples of unilateral memory traces, it seems safe to surmise that bilaterality is the most common mode. That does not, of course, mean that the effects of hemispheric specialization in human subjects plays no role. In fact, the observations of Kavcic and Doty (2002) show that words seen initially *via* the left visual field are subsequently recognized better *via* the right than *via* the initial left visual field, suggesting that although the initial input was *via* the right hemisphere, the memory was best evoked *via* the left.

INDEPENDENT ENTITIES

Although sporadic reports of survival after loss of one cerebral hemisphere are found in the 19th Century (see Smith 1974, Smith and Sugar 1975), it is the 20th Century that will be known for the profound discovery that the human mind exists in duplicate. Thanks to Krynauw's (1950) bold and successful treatment by hemispherectomy of children suffering uncontrollable seizures and hemiplegia there are now several hundred individuals living relatively normal lives with only one cerebral hemisphere. While the original neurological deficiency often leaves its mark upon the ultimate recovery from this drastic surgery, there are many dramatic cases for whom a single hemisphere is sufficient for an essentially normal mental life (e.g., Battro 2000, Gott 1973, Ogden 1996a,b, Schepelmann et al. 1976, Vargha-Khadem et al. 1997), some even attaining University training and professional status (Griffith and Davidson 1966, Smith and Sugar 1975). Most unexpected has been the extensive development of speech and linguistic skill in cases lacking the left hemisphere, perhaps because the damage to that hemisphere occurs early in life, allowing full development of an otherwise incipient skill in the right hemisphere. Of course, a complete brain is better than half; yet the deeper lesson is that bilateral symmetry does produce two nearly equivalent, and potentially independent, conscious entities.

The other side of the discovery of this remarkable fact has been the demonstration that the two entities can indeed simultaneously pursue relatively independent mental lives. As previously summarized (Doty 1999), this discovery resulted from a most fortuitous chain of events: Sperry's demonstration in fish, with fully crossed visual paths (Sperry and Clark 1949), that a habit learned with one eye was accessible *via* the other; then the extension with his student, Myers (Myers and Sperry 1953), that the same was true of mammals if the callosum were present and the optic chiasm cut; followed subsequently by the therapeutic surgery, performed by Myers' friend, Bogen (Bogen and Vogel 1962), transecting the forebrain commissures of a wounded veteran in desperate need of relief from intractable epilepsy; to reveal the heretofore unknown "split-brain" condition (Gazzaniga et al. 1962).

Leaving aside the complexities of hemispheric specialization and shortcomings of life with half a brain, the enduring fascination with these findings is that they unequivocally demonstrate that a human mind is achieved by either hemisphere, that transecting the forebrain commissures releases within each hemisphere a mind independent of its partner and, *ipso facto*, normal human mentality is a composition, held together by the ancient bonds required to assure the functionality of bilateral symmetry. This profound and inescapable fact must henceforth channel contemplation of the nature of man, of consciousness, and how free will can be partitioned between such contending entities.

The further conclusion is that the fibers of the forebrain commissures are the means by which the ineffable unity of mind is created from the individual experiences of each hemisphere. The continuous necessity for this interhemispheric exchange is now readily seen in the bihemispheric activity revealed with fMRI in a great variety of mental tasks (e.g., Kavcic et al. submitted).

WHAT HAPPENS IN THE BRAINSTEM?

While all of the foregoing is true, an equally profound fact is that the forebrain is useless without input from pontine and mesenecephalic systems (Plum and Posner 1982); and the power of these inputs is evident daily in the unconsciousness of sleep and the bizarre mentality of dreams. In the past 50 years these brainstem systems have been studied in great detail (see, e.g., Doty 1995 for review), as merits their importance, and four major components projecting to neocortex have been identified, each characterized by a different neurotransmitter/modulator: the locus coeruleus, norepinephrine; the serotonergic system of the raphé; the ventral tegmental area, dopamine; and possibly to some degree the pedunculopontine-laterodorsal tegmental complex, but mostly the nucleus basalis, acetylcholine (Saper 1990). Each of these systems in turn is under control from neocortex so that, in essence, a multifarious loop exists, circulating activity from brainstem to cortex and back. Indeed, when cortical input is removed, much of the mesencephalon falls silent (Żernicki et al. 1970).

To this list has now been added orexin that, in a sense, seems to be the "juice of free will"! Mice, dogs, and man lacking orexin(s) of the lateral hypothalamus are prone to collapse in a state of cataplexy (narcolepsy) (Chemelli et al. 1999, Lin et al. 1999, Peyron et al. 1998, Thakkar et al. 1999, Thannickal 2000). The family of peptides of which orexin is a member has been in existence since at least the origin of fishes (Alvarez and Sutcliffe 2002). In the mammalian brain the orexin neurons are found only in the lateral hypothalamus, but they project throughout the brain, including neocortex and spinal cord, and impinge with particular richness upon the locus coeruleus and raphé (see de Lecea et al. 2002, Willie et al. 2001 for reviews). Their activity is clearly associated with movement, rather than with feeding, the context in which they were discovered.

The serotonergic raphé is of particular note in relation to interhemispheric processing. Upon injecting horseradish peroxidase liberally into the striate cortex of macaques it became apparent that cells on both sides of the raphé were marked, 25-45% being contralateral to the injection (Doty 1983, Wilson and Molliver 1991). In other words, both sides of the raphé project to each side of neocortex, thus assuring a unique bilaterality in its influence.

What this bilaterality may contribute to unification of events in the two hemispheres is still but a matter for speculation. Nevertheless, there is clear evidence that such unification can, to some degree, proceed at brainstem levels even in the absence of the forebrain commissures; but the locus or mechanism thereof remains unexplored. In "split-brain" macaques there has been a consistent finding that when the same visual item is simultaneously presented to be recognized by each of the divided hemispheres, performance (accuracy) exceeds that obtained when either hemisphere is questioned alone; but not if the two items are discrepant (Kavcic et al. 2000, Nakamura and Gazzaniga 1977, Ringo et al. 1991). A possibly related instance of bilateral processing in the brainstem of "split-brain" macaques was reported by Lewine et al. (1994). It involved "loading" the hemispheres with one to six visual items to be remembered. Following the well-known paradigm of Sternberg (1969), the reaction time to designate whether a subsequently presented item was or was not a member of a to-be-remembered set, was proportional to the number of items in the set. When either the anterior commissure or the splenium of the corpus callosum were intact, the reaction times in macaques were independent of which hemisphere had viewed which items of the set initially; but in the case of complete transection of the forebrain commissures the subsequent reaction time depended solely upon the number of items that had been presented initially to the queried hemisphere. In other words, the commissures unified the mnemonic load, but in their absence each hemisphere reacted according to the load that it, individually, had acquired. However, the more unexpected finding was that in the latter case the accuracy of either hemisphere depended upon the combined load held by the two together, even though the reaction time went according to their individual load. Thus, presumably, there is some "resource" at the brainstem level that is limited and shared for achieving the accuracy of recognition (Lewine et al. 1994).

Further evidence for brainstem participation in resolution of events transpiring in the separated (split-brain) hemispheres of macaques has been provided by presenting to-be-remembered visual items simultaneously to each hemisphere (Kavcic et al. 2000). The level of resulting memory was then compared to that established when each hemisphere acted alone at encoding and retrieval. First, it was clear that "parallel processing" could be highly efficient, even if different images were viewed by each hemisphere, since accuracy exceeded that of each hemisphere acting alone on each occasion. On the other hand, if each viewed an image initially, but then only one hemisphere was queried, accuracy was less than that found when items were presented to a single hemisphere on each occasion. It can be argued that here accuracy is diminished not only because the idle, nonqueried hemisphere interferes, but also because the initial bilateral presentation had established a bilateral subcortically available trace that is discordantly matched by presentation of but half of it. The reality of such possibility is promoted by findings of Marcel (1998) that patterns projected into a hemianopic field can influence what such a patient sees.

If, in the Kavcic et al. (2000) experiments, one hemisphere has seen an item and then it is re-presented to that hemisphere at the same time that the other hemisphere views an item that it has not previously seen, an insoluble conflict is established between the hemispheres as to what the response should be to the mnemonic query. Paralysis does not result. True to the demands of functionally sustainable bilateral symmetry, one or the other hemisphere seizes control of the motor apparatus (ocular motility in this case) to achieve the response appropriate to its view of things. To prevent establishment of such a simple dominance pattern, where one hemisphere comes to respond on each occasion of conflict, the situation was arranged so that it was soluble: for several weeks the response "previously seen" was always rewarded, and then for several more weeks changed to consistently rewarding the response "not previously seen". Although dominance did appear, the two hemispheres were also able to achieve a *modus operandi* whereby reward was obtained at levels considerably above chance. In other words, through feedback, from the action each had intended *versus* what action was rewarded, an accommodation was gradually achieved as to parcellating action according to some subcortical comparison.

CONCLUSIONS

The foregoing facts severely constrain speculation as to the coupling between neuronal activity and human mentation. Given that callosal fibers are essential to the unification of bihemispheric action and perception, nerve impulses are the *sine qua non* of the process, and field effects are inadequate. By their nature, however, the spatiotemporal spread of these transactions, as well as of those throughout each hemisphere, propound the ultimate riddle, as to how the fusion of these multimillioned evanescent fluxes yield the continuous, richly detailed, fabric of each mental moment.

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Received 15 May 2003, accepted 22 May 2003